Patent
Attorney's Docket No. 002010-596

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

THORSETT et al.

Application No.: unassigned

Filed: herewith

For: CARBAMYL COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

Group Art Unit: unassigned

Examiner: unassigned

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

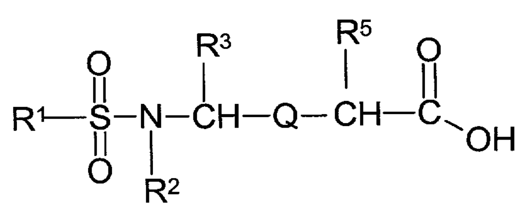
Prior to the examination of the above-noted application, entry of the following amendments is respectfully requested. Prior to the entry of this amendment, Claim 1 is pending in this application. A marked up version showing the amendments is attached.

AMENDMENTS

In the Claims:

Please amend Claim 1 as follows:

1. A compound of formula I:



I

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

$-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

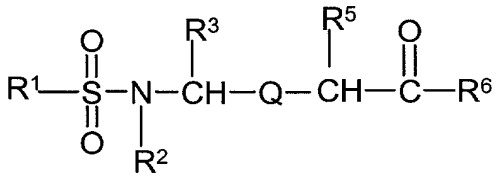
x is an integer of from 1 to 4;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Please add new claims 35-59 as follows:

35. A compound of formula IA:



IA

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ and $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

$-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

36. A compound according to Claims 1 or 35 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

37. A compound according to Claims 1 or 35 wherein R^1 is selected from the group consisting of methyl, isopropyl, *n*-butyl, benzyl, phenethyl, phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, $4-(H_2NC(O)-)$phenyl, $4-(H_2NC(S)-)$phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, $4-(CH_3C(O)NH-)$phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, $4-(CH_3SC(=NH)-)$phenyl, $4-chloro-3-(H_2NS(O)_2-)$phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl,

pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, morpholin-4-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methylimidazol-4-yl, 1-N-methylpyrazol-3-yl, 1-N-methylpyrazol-4-yl, 1-N-butylpyrazol-4-yl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

38. A compound according to Claims 1 or 35 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-ϕ.

39. A compound according to Claims 1 or 35 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylmethyl, -CH_2CH_2-COOH, -CH_2-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH_2O-benzyl and hydroxymethyl.

40. A compound according to Claims 1 or 35 wherein Q is -C(O)NH- or -C(S)NH-.

41. A compound according to Claims 1 or 35 wherein Ar is aryl or substituted aryl.

42. A compound according to Claim 41 wherein Ar is phenyl or substituted phenyl and *x* is 1.

43. A compound according to Claim 1 or 35 wherein R^5 is selected from the group consisting of

3-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NS(O)_2O$-]benzyl,

4-[(piperidin-1′-yl)C(O)O-]benzyl,

4-[(piperidin-4′-yl)C(O)O-]benzyl,

4-[(1′-methylpiperidin-4′-yl)C(O)O-]benzyl,

4-[(4′-hydroxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-formyloxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-ethoxycarbonylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-carboxylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(3′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenyl-1′-Boc-piperidin-4′-yl)-C(O)O-]benzyl,

4-[(4′-piperidon-1′-yl ethylene ketal)C(O)O-]benzyl,

4-[(piperazin-4′-yl)-C(O)O-]benzyl,

4-[(1′-Boc-piperazin-4′-yl)-C(O)O-]benzyl,

4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methylhomopiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(2-hydroxyethyl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(4-trifluoromethylpyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyrimidin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-acetylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-4-ylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(S)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(4′-trifluoromethanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(morpholin-4′-yl)C(O)O-]benzyl,

3-nitro-4-[(morpholin-4′-yl)-C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl)C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl sulfone)-C(O)O-]benzyl,

4-[(pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-methylpyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(methoxycarbonyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(hydroxymethyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(N,N-dimethylamino)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2′-(N-methyl-N-toluene-4-sulfonylamino)ethyl)(CH_3)N-C(O)O-]benzyl,

4-[(2′-(morpholin-4′-yl)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2′-(hydroxy)ethyl)(CH_3)NC(O)O-]benzyl,

4-[bis(2′-(hydroxy)ethyl)NC(O)O-]benzyl,

4-[(2′-(formyloxy)ethyl)(CH_3)NC(O)O-]benzyl,

4-[($CH_3OC(O)CH_2$)HNC(O)O-]benzyl,

4-[2′-(phenylNHC(O)O-)ethyl-]HNC(O)O-]benzyl,

3-chloro-4-[($(CH_3)_2$NC(O)O-]benzyl,

3-chloro-4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(thiomorpholin-4′-yl)C(O)O-]benzyl, and

3-fluoro-4-[($(CH_3)_2$NC(O)O-]benzyl.

44. A compound according to Claim 35 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy, 2-α-isopropyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, -$O(CH_2CH_2O)_2CH_3$, 2-(phenoxy)ethoxy, -$OCH_2C(CH_3)_2$NHBoc, -NH_2, benzyloxy, -$NHCH_2COOH$, -$NHCH_2CH_2COOH$, -NH-adamantyl, -$NHSO_2$-*p*-CH_3-ϕ, -$NHCH_2CH_2COOCH_2CH_3$, -NHOY′ where Y′ is hydrogen, methyl, *iso*-propyl or benzyl, -O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, -OCH_2-$OC(O)C(CH_3)_3$, -$O(CH_2)_z$NHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -

NR″C(O)-R′ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or -$CH_2C(O)OCH_2CH_3$.

45. A compound selected from the group consisting of:

N-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(isonipecotoyloxy)phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-*N*-methyl-2-(*tert*-butyl)glycinyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

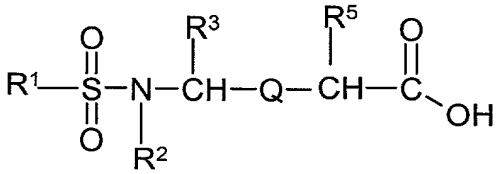
3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-carboxy-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine *tert*-butyl ester

N-(methanesulfonyl)-*N*-benzylglycinyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine tert-butyl ester

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester, *tert*-butyl ester and neopentyl ester.

46. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I:



I

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

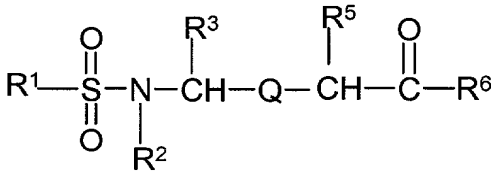
Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

47. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula IA:



IA

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ and $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

48. A pharmaceutical composition according to Claims 46 or 47 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

49. A pharmaceutical composition according to Claims 46 or 47 wherein R^1 is selected from the group consisting of methyl, isopropyl, *n*-butyl, benzyl, phenethyl, phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-)phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-($CH_3SC(=NH)$-)phenyl, 4-chloro-3-($H_2NS(O)_2$-)phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, morpholin-4-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methylimidazol-4-yl, 1-N-methylpyrazol-3-yl, 1-N-methylpyrazol-4-yl, 1-N-butylpyrazol-4-yl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

50. A pharmaceutical composition according to Claims 46 or 47 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-ϕ.

51. A pharmaceutical composition according to Claims 46 or 47 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylmethyl, $-CH_2CH_2-COOH$, $-CH_2-COOH$, 2-amidoethyl, *iso*-butyl, *t*-butyl, $-CH_2O$-benzyl and hydroxymethyl.

52. A pharmaceutical composition according to Claims 46 or 47 wherein Q is -C(O)NH- or -C(S)NH-.

53. A pharmaceutical composition according to Claims 46 or 47 wherein Ar is aryl or substituted aryl.

54. A pharmaceutical composition according to Claim 53 wherein Ar is phenyl or substituted phenyl and *x* is 1.

55. A pharmaceutical composition according to Claim 46 or 47 wherein R^5 is selected from the group consisting of

3-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NS(O)_2O$-]benzyl,

4-[(piperidin-1′-yl)C(O)O-]benzyl,

4-[(piperidin-4′-yl)C(O)O-]benzyl,

4-[(1′-methylpiperidin-4′-yl)C(O)O-]benzyl,

4-[(4′-hydroxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-formyloxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-ethoxycarbonylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-carboxylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(3′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenyl-1′-Boc-piperidin-4′-yl)-C(O)O-]benzyl,

4-[(4′-piperidon-1′-yl ethylene ketal)C(O)O-]benzyl,

4-[(piperazin-4′-yl)-C(O)O-]benzyl,

4-[(1′-Boc-piperazin-4′-yl)-C(O)O-]benzyl,

4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methylhomopiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(2-hydroxyethyl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(4-trifluoromethylpyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyrimidin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-acetylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-4-ylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(S)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(4′-trifluoromethanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(morpholin-4′-yl)C(O)O-]benzyl,

3-nitro-4-[(morpholin-4′-yl)-C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl)C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl sulfone)-C(O)O-]benzyl,

4-[(pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-methylpyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(methoxycarbonyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(hydroxymethyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(N,N-dimethylamino)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2′-(N-methyl-N-toluene-4-sulfonylamino)ethyl)(CH_3)N-C(O)O-]benzyl,

4-[(2′-(morpholin-4′-yl)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2′-(hydroxy)ethyl)(CH_3)NC(O)O-]benzyl,

4-[bis(2′-(hydroxy)ethyl)NC(O)O-]benzyl,

4-[(2′-(formyloxy)ethyl)(CH_3)NC(O)O-]benzyl,

4-[($CH_3OC(O)CH_2$)HNC(O)O-]benzyl,

4-[2′-(phenylNHC(O)O-)ethyl-]HNC(O)O-]benzyl,

3-chloro-4-[($(CH_3)_2$NC(O)O-]benzyl,

3-chloro-4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(thiomorpholin-4′-yl)C(O)O-]benzyl, and

3-fluoro-4-[($(CH_3)_2$NC(O)O-]benzyl.

56. A pharmaceutical composition according to Claim 47 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy, 2-α-isopropyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, -$O(CH_2CH_2O)_2CH_3$, 2-(phenoxy)ethoxy, -$OCH_2C(CH_3)_2$NHBoc, -NH_2, benzyloxy, -$NHCH_2COOH$, -$NHCH_2CH_2COOH$, -NH-adamantyl, -$NHSO_2$-*p*-CH_3-ϕ, -$NHCH_2CH_2COOCH_2CH_3$, -NHOY′ where Y′ is hydrogen, methyl, *iso*-propyl or benzyl, -O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, -OCH_2-$OC(O)C(CH_3)_3$, -$O(CH_2)_z$NHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR″C(O)-R′ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or -$CH_2C(O)OCH_2CH_3$.

57. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claim 1 or 35 under conditions wherein said compound binds to VLA-4.

58. A method for treating an inflammatory condition in a mammalian patient which condition is mediated by VLA-4 which method comprises administering to said

patient a therapeutically effective amount of a pharmaceutical composition of Claim 46 or 47.

59. The method according to Claim 58 wherein said inflammatory condition is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury.

Conclusion

Early examination on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

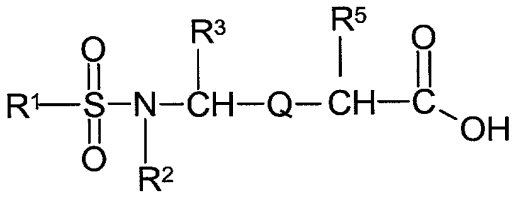
By: _____
Leslie J. Boley
Registration No. 41,490

P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300

Date: November 14, 2001

Marked Up Version Showing Amendments

1. A compound of formula I:



I

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, **and** substituted heteroaryl**[**, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group**]**;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, **and** substituted heterocyclic **[**and, when R^2 does not form a heterocyclic group with R^1, R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a heterocyclic or a substituted heterocyclic group**]**;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

$-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.